

A Phase III Randomized, Double Blind, Placebo-controlled, Multicenter, Parallel Group Study to Assess the Efficacy and Safety of Fixed-dose Combination RHB-104 in Subjects with Moderately to Severely Active Crohn's Disease

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Principal Investigator: [REDACTED]

Sponsor's Medical Director: [REDACTED]

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Statement of Confidentiality

The information contained in this document is confidential and is not to be disclosed without the express consent of RedHill Biopharma Ltd.

STATEMENT OF COMPLIANCE

This study will be carried out in accordance with Good Clinical Practices (GCP) as identified and/or required by the following regulations and guidance:

- Declaration of Helsinki (Tokyo, 2004)
- US Code of Federal Regulations: 45 CFR Part 46, 21 CFR Parts 50, 56, and 312
- Canadian Food and Drug Regulations F-27 – C.R.C., c. 870: Division 5 (C.05.)
- ICH E6; Consolidated Guidelines on Good Clinical Practices (1997)
- Appropriately identified sponsor/CRO and local clinical SOPs

Title:	A Phase III Randomized, Double Blind, Placebo-controlled, Multicenter, Parallel Group Study to Assess the Efficacy and Safety of Fixed-dose Combination RHB-104 in Subjects with Moderately to Severely Active Crohn's Disease
Phase:	Phase III
Study Population:	<p>Subjects with active, moderate to severe Crohn's Disease (CD).</p> <p>The following inclusion criteria apply:</p> <ul style="list-style-type: none"> • Males and females 18 to 75 years of age. • Signed fully informed consent provided as per this protocol. • Diagnosis of Crohn's Disease confirmed by endoscopy or radiography and/or histology at least 6 months prior to randomization into the study. • CD involving the ileum and/or colon • Moderately to severely active CD (Crohn's Disease Activity Index (CDAI) score of ≥ 220 and ≤ 450) at baseline. • Current treatment with at least one of the following therapies: <ul style="list-style-type: none"> ○ Oral 5-aminosalicylic acid (5-ASA) compounds <ul style="list-style-type: none"> ▪ Dose must be stable for at least 4 weeks before baseline ○ Corticosteroid therapy <ul style="list-style-type: none"> ▪ Dose must be stable for at least 2 weeks before baseline ○ Azathioprine or 6-mercaptopurine (6-MP) or methotrexate <ul style="list-style-type: none"> ▪ Dose must be stable for at least 8 weeks before baseline ○ Infliximab or adalimumab <ul style="list-style-type: none"> ▪ Dose must be stable for at least 14 weeks before baseline • White blood cell count $\geq 3.5 \times 10^9$ at screening. • Active Crohn's disease, defined by at least one of the following: C-reactive protein > Upper Limit of Normal (ULN) at screening, fecal calprotectin > Upper Limit of Normal (ULN) at screening, OR radiographic (MRE or CTE) or endoscopic confirmation of the presence of <u>active</u> CD within 5 weeks of screening visit. • Subject agrees to use the following effective contraceptive methods only <ul style="list-style-type: none"> ○ diaphragm, cervical cap, contraceptive sponge or condom with spermicidal foam/gel/cream/suppository ○ IUD/IUS ○ progestogen injection (Depo-Provera®) <p>throughout the study and for at least 6 weeks after last study drug administration, unless subject or partner of subject is post-menopausal or otherwise incapable of becoming pregnant by reason of surgery or tubal ligation, or has had a vasectomy. In regions where local regulatory contraceptive requirements differ, the ICF will reflect local policies.</p> <p>The following key exclusion criteria apply:</p> <ul style="list-style-type: none"> • Crohn's disease involvement isolated to the mouth, upper gastrointestinal tract, or anus.

	<ul style="list-style-type: none"> • History of total colectomy with ileorectal anastomosis or a proctocolectomy. • Presence of active fistulizing Crohn's Disease or healed fistula within 2 months prior to screening. • Subject has postoperative stoma, ostomy, or ileoanal pouch. • Subject has short bowel syndrome. • Subject is scheduled for surgical bowel resection. • Subject has known symptomatic obstructive strictures or bowel perforation in the 6 months prior to screening. • Change in dose or discontinuation of oral 5-aminosalicylic acid (5-ASA) compounds less than 4 weeks prior to baseline. • Change in dose or discontinuation of corticosteroids less than 2 weeks prior to baseline. • Change in dose or discontinuation of azathioprine, 6-mercaptopurine (6-MP) or methotrexate less than 8 weeks prior to baseline. • Change in dose or discontinuation of infliximab or adalimumab less than 14 weeks prior to baseline. • Treatment with vedolizumab less than 120 days prior to baseline or biological therapies (apart from infliximab or adalimumab) less than 60 days prior to baseline. • Previous treatment with rifabutin and/or clofazimine. • Oral or parenteral antibiotics in the 4 weeks prior to baseline (topical antibiotics are permitted). • Treatment with probiotics (excluding yogurt and yogurt-derived products) in the 4 weeks prior to baseline. • Females who have a positive pregnancy test or are lactating.
Number of Subjects:	Estimated total: 410 subjects, curtailed to 324 with Protocol Version 11.0, will be randomized into the study.
Number of Sites:	The study will be conducted at up to 150 sites in the USA, Canada, Israel, Australia, New Zealand, Poland, Bulgaria, Czech Republic, Romania, Slovakia and Serbia.
Study Design:	<p>This study is a multicenter, Phase III, randomized, placebo-controlled, double-blind study designed to evaluate the efficacy and safety of RHB-104 compared to placebo to treat subjects with moderate to severe CD. RHB-104 consists of 3 antibiotics with activity against <i>Mycobacterium avium subsp. paratuberculosis</i> (MAP), a potential cause of CD. Subjects with active CD will be randomized at baseline in a 1:1 fashion to receive up to 52 weeks of RHB-104 or placebo. Randomization will be performed within strata defined by whether subjects use protocol permitted anti-TNF agents (yes or no). Subjects will remain on stable doses of their baseline CD treatment although steroids may be tapered after Week 8 at the discretion of the investigator.</p> <p>The study is designed to assess remission at Week 26 as the primary endpoint. However, as MAP are slow growing mycobacteria without a proven antibiotic treatment, the duration of antibiotic treatment needed to achieve remission in subjects with CD caused by MAP may be longer than 26 weeks. Subjects with response at week 26 may ultimately achieve remission at a later time point with continued treatment for MAP. Also, subjects with CD treated for underlying MAP infection may experience benefits with a longer period of time in response or remission with RHB-104 treatment compared to placebo. Thus, the study is also designed to assess response, remission, and maintenance of remission in subjects on randomized treatment through week 52.</p>

	<p>Blood samples will be collected at baseline and at every visit after the initial 4 weeks of treatment to test for MAP in the serum using a polymerase chain reaction (PCR) assay. MAP cultures will be prepared from whole blood collected at the baseline visit and after 26 and 52 weeks of treatment.</p> <p>Safety and pharmacokinetics of the fixed-dose combination product, RHB-104, will also be assessed.</p> <p>Colonoscopy will be done in consenting subjects prior to initiation of study drug and after 26 weeks of study drug to assess for mucosal healing as well as MAP status via PCR and culture. Optional biopsies will also be collected for possible measurement of tissue drug levels and archived for future MAP determinations.</p> <p><u>Study Visit Schedule:</u></p> <p>Screening, baseline, and follow-up visits at weeks 2, 4, 6 (+/- 3 days), 8, 12, 16, 20, 26, 35, 44, 52, and 56 (+/- 7 days). Subjects undergoing colonoscopy will have a procedural visit after week 26 assessment so as to not interfere with data collection.</p>												
Subject Participation Duration:	Subjects are expected to participate up to 62 weeks. However, subjects who complete 26 weeks of study drug administration and remain out of remission e.g. CDAI ≥ 150 , will be eligible for open label treatment with RHB-104 in an extension study (protocol RHB-104-04). Subjects may elect to continue in the RHB-104-01 study, and will remain in the RHB-104-01 study until study drug administration in the RHB-104-04, if applicable.												
Treatment:	RHB-104; a fixed-dose combination of 95 mg clarithromycin, 45 mg rifabutin, and 10 mg clofazimine. Placebo is a capsule with a similar appearance as RHB-104.												
Route of Administration:	Oral capsule.												
Dosage Regimen for Investigational Product:	<p>The target dose of RHB-104 will be 5 capsules administered bid.</p> <p>In order to reach this target with minimal adverse effects, the subject's dose will be titrated up over the first 4 weeks of treatment, and the dose will remain stable thereafter (see schedule below). Subjects randomized to placebo will receive the same number of capsules as the RHB-104 group according to the schedule below. The study drug will be taken with food. Subjects who fail dose escalation to 5 capsules bid will be considered treatment failures and withdrawn from the study.</p> <p>Dose Titration by Week for initiating RHB-104</p> <table border="1"> <thead> <tr> <th>Week</th> <th>1</th> <th>2</th> <th>3</th> <th>4</th> <th>5-52</th> </tr> </thead> <tbody> <tr> <td>Study Drug</td> <td>1 capsule bid</td> <td>2 capsules bid</td> <td>3 capsules bid</td> <td>4 capsules bid</td> <td>5 capsules bid</td> </tr> </tbody> </table>	Week	1	2	3	4	5-52	Study Drug	1 capsule bid	2 capsules bid	3 capsules bid	4 capsules bid	5 capsules bid
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Outcome Measures	<p>Remission (primary outcome measure) – Remission in a subject is defined as a CDAI score of < 150.</p> <p>Response – A response in the individual subject is defined as reduction in CDAI score of ≥ 100 from baseline.</p> <p>Time to remission – The time (weeks after randomization) that a subject first records a state of remission.</p> <p>Duration of remission – The time that a subject is in a state of remission.</p> <p>Time to response – The time (weeks after randomization) that a subject first achieves a state of response.</p> <p>Duration of response – The time that a subject is in a state of response.</p> <p>Maintenance of Remission – Remission in a subject from week 26 through week 52.</p>												

	<p>Other Outcome Measures</p> <p>MAP Detection:</p> <ul style="list-style-type: none"> • Proportion of randomized subjects with a MAP positive blood PCR assay at baseline • Proportion of subjects with a change in MAP blood PCR assay status after 26 weeks of treatment compared to baseline • Proportion of subjects with a change in MAP blood PCR assay status after 52 weeks of treatment compared to baseline • Sequential comparison of MAP blood PCR assay results per subject • Proportion of randomized subjects with a MAP positive blood culture at baseline • Proportion of subjects with a change in MAP blood culture status after 26 weeks of treatment compared to baseline • Proportion of subjects with a change in MAP blood culture status after 52 weeks of treatment compared to baseline • Proportion of randomized subjects with a MAP positive colon biopsy PCR assay at baseline • Proportion of subjects with a change in MAP positive colon biopsy PCR assay status after 26 weeks of treatment compared to baseline • Proportion of randomized subjects with a MAP positive colon biopsy culture at baseline • Proportion of subjects with a change in MAP positive colon biopsy MAP culture status after 26 weeks of treatment compared to baseline • These measures of MAP status will be assessed for diagnostic performance against MAP culture as the definitive status measure. Performance measures include sensitivity and specificity and other measures of diagnostic performance derived there from, and will be computed by arm for assessments from samples following initiation of study intervention. <p>Endoscopic Changes in Those Subjects Who Undergo Colonoscopy:</p> <ul style="list-style-type: none"> • Change from baseline in the mean Crohn's Disease Endoscopic Index of Severity (CDEIS and SES-CD) after 26 weeks of treatment • Correlation between the change from baseline in the endoscopic index (ΔCDEIS and ΔSES-CD) and the clinical index (ΔCDAI) after 26 weeks of treatment <p>Health-Related Quality-of-life (HRQoL):</p> <ul style="list-style-type: none"> • Change from baseline in the SF-36 questionnaire total score and domain scores • Change from baseline in the mean Inflammatory Bowel Disease Questionnaire (IBDQ) score <p>Inflammation:</p> <ul style="list-style-type: none"> • Changes from baseline in a serum marker of inflammation: C-reactive Protein (CRP) • Changes from baseline in a stool marker of inflammation: fecal calprotectin
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<p>Objectives:</p>	<p>Primary Objective The primary objective is to assess whether subjects randomized to receive RHB-104 have a higher probability of being in a state of remission at the 26 week assessment as compared to subjects randomized to receive placebo.</p> <p>Key Secondary Objectives</p> <ol style="list-style-type: none"> 1. Assess whether subjects randomized to receive RHB-104 have a higher probability of being in a state of response at the 26 week assessment as compared to subjects randomized to receive placebo. 2. Assess whether subjects randomized to RHB-104 have a higher probability of being in a state of remission at the 52 week assessment as compared to subjects randomized to receive placebo 3. Assess whether subjects randomized to RHB-104 have a higher probability of being in a state of remission in assessments from week 26 through week 52 as compared to subjects randomized to receive placebo 4. Assess whether subjects randomized to receive RHB-104 have a higher probability of being in a state of remission at the 16 week assessment as compared to subjects randomized to receive placebo 5. Assess whether subjects randomized to receive RHB-104 have a higher probability of being in a state of steroid free remission at the 52 week assessment as compared to subjects randomized to receive placebo. Subjects must be maintained off steroids for 3 weeks in order to be determined to be in steroid free remission e.g. by week 49. <p>Selected Other Supportive Objectives</p> <ol style="list-style-type: none"> 1. To compare the arm-specific time to remission and response. 2. To compare the arm-specific duration of remission and response. 3. To compare the proportion of subjects who have maintained remission from week 16 through week 52. 4. Assess whether subjects randomized to receive RHB-104 have a higher probability of being in a state of response at the 16 week assessment as compared to subjects randomized to receive placebo. 5. To assess the difference between arms in health-related quality-of-life using the IBDQ and SF-36 questionnaire. 6. To compare arm-specific endoscopic 26-week changes using the CDEIS and SES-CD score in those subjects who consent to undergo colonoscopy 7. To assess the effect of RHB-104 on markers of inflammation. 8. To assess the proportion of subjects in steroid free remission in each treatment arm at weeks 26. Subjects must be maintained off steroids for 3 weeks in order to be determined to be in steroid free remission e.g. by week 23 <p>Other Exploratory Objectives</p> <ol style="list-style-type: none"> 9. To characterize the pharmacokinetic profiles of each of the active agents (and active metabolites for clarithromycin and rifabutin) using a population PK approach.

	<p>10. To assess the efficacy outcome measures for interaction with the baseline assay results for MAP infection (positive versus negative) to use in development of MAP blood PCR testing.</p> <p>11. To compare the arm-specific changes in MAP PCR status (positive to negative) from pre- to post-treatment at week 26 and week 52.</p> <p>12. To compare arm-specific 26-week change from baseline in the endoscopic index (ΔCDEIS and ΔSES-CD) and the clinical index (ΔCDAI).</p> <p>13. To compare the arm-specific changes in MAP culture status (positive to negative) from pre- to post-treatment at week 26 and week 52.</p> <p>14. To assess the tissue levels of the active agents of RHB-104 in colon biopsy samples if possible.</p> <p>Safety Objective: Assess the safety impact of treatment with RHB-104.</p>
<p>Study Completion:</p>	<p>Upon completion of clinical activities and safety follow-up.</p>
<p>Statistical Considerations</p>	<p>Using data published by Sandborn et al. (2013), it was determined that the placebo rate of remission would be 21%. Using this information, the overall power and sample size calculations have been modified since the original assumptions concerning overall remission rates were different. Using this new information, it is proposed that a total of 410 patients (205 per group) be enrolled. There will still be one stratification factor in this design – use of protocol permitted anti-TNF agents (yes/no). With this sample size there is 90% power (with $\alpha=0.05$ 2-sided) to detect a difference between groups i.e. placebo and RHB-104, assumed that the observed difference will be 15% in absolute percent. The proportion of remission success is assumed to be 21% in the Placebo group and 36% (or higher) in the treatment group. The test statistic used for this analysis will be a two-sided Cochran-Mantel-Haenszel (CMH) test controlling for the stratification variable (anti-TNF agents (yes/no) under the ITT principle. These calculations were made to allow for two sequential tests to be made using the O'Brien-Fleming spending function to determine the test boundaries. The interim analysis (first sequential test) will occur when 50% of the patients have their outcome data measured (i.e., reach 26 weeks of follow-up). The 2-sided alpha level for stopping the trial for efficacy at the interim analysis is 0.003. If this criterion is not met the trial will be continued and the final analysis (second sequential test) will be performed using a 2-sided alpha level of 0.049 for testing the primary outcome. In all analyses, subjects with missing 26 week assessments will be assumed to not be in a state of remission at 26 weeks. Furthermore, the primary assessment will be for all subjects randomized according to randomized group (intent-to-treat). It should be noted that the anticipated effect of the intervention will be a 15% improvement in 26-week remission success, however a clinically meaningful difference in this measure (26 week remission success proportion) is 9% (in absolute percent) based on clinical expert opinion. Therefore, any statistically significant difference between groups that has an observed percent difference of 9% or larger would indicate that treatment is effective.</p> <p>Protocol Version 11.0 curtails the number of expected enrolled patients to 324 (162 per group). Final analysis of the data is to be carried out when approximately 324 patients have completed the Week 26 primary endpoint assessment. This sample size curtailment reflects the study's current accrual trends. The anticipated power will be at least 80% given the study design stage assumptions regarding the treatment groups primary efficacy endpoint (36% RHB-104 vs. 21% Placebo).</p> <p>The secondary endpoints will be analyzed under the ITT approach to be described in detail in the Statistical Analysis Plan</p>